Original Article

Evaluation of Myelosupression during Imatinib Mesylate Therapy in Patients with Chronic Myeloid Leukaemia

Khan L[1], Salsabil MA[2], Ferdous J[3], Haque MR[4]

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Abstract

Introduction: Chronic Myloid Leukaemia (CML) is a myeloproliferative neoplasm that originates in an abnormal pluripotent stem cell. Imatinib, a tyrosine kinase inhibitor, is the drug of choice for CML in the present time. During therapy, a few patients develop myelosuppression and present with cytopenias.

Objectives: To evaluate myelosupression during therapy with Imatinib mesylate in patients with Chronic myloid leukaemia in chronic phase.

Materials and Methods*:* This cross sectional observational study was carried out at department of Haematology, Combined Military Hospital, Dhaka and Haematology OPD, Bangabandhu Sheikh Mujib Medical University (BSMMU) from October 2011 to September 2012. A total of 30 patients fulfilling the inclusion criteria were included in this study. Data were collected in a structured proforma, analyzed with SPSS and expressed in mean, frequency and percentage.

Results: Patients mean age was 38.96±9.37 years ranging from 23 to 56 years. Among 30 study subjects, male and female patients were 22(73%) and 08(27%) respectively. Most of the patients presented with generalized weakness (83.3%), weight loss (53.3%), fever (26.7%), pain abdomen (36.6%) and fullness of abdomen (33.3%). Twenty (66.67%) cases develop anaemia, 02(10%) cases leucopenia, 07(23.33%) cases thrombocytopenia and 11(36.6%) patients develop different combination of bicytopenia and 2% patients developed pancytopenia after being treated with Imatinib.

Conclusion: Various degrees of myelosupression with cytopenias may occur in few patients of CML on Imatinib therapy. Regular hematologic follow-up is required so that the drug may be stopped or dose modified as per the individual's needs.

Key-words: Chronic Myloid Leukaemia, Pluripotent stem cell**,** Imatinib, Myelosupression.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that originates in an abnormal pluripotent stem cell[1]. This altered stem cell proliferates and generates a population of differentiated cells that gradually displaces normal haemopoiesis and leads to a greatly expanded total myeloid mass. It is characterized by the presence of a BCR-ABL fusion gene, which is the result of a reciprocal translocation between chromosome 9 and 22, cytogenetically visible as a shortened chromosome 22 (Philadelphia [Ph] chromosome)[2]. Imatinib (Gleevec, Novartis; formerly called STI571) is a relatively specific inhibitor of the BCR-ABL tyrosine kinase and is used for targeted treatment of CML[3].

Myelosuppression in patients receiving therapy (may manifest as anemia, neutropenia and thrombocytopenia) has been identified as an independent adverse risk factor for achieving a good cytogenic response[4]. Selective inhibition of predominantly Philadelphia chromosome (Ph+) driven haematopoiesis may explain myelosuppression in CML. Myelosuppression developing during therapy may have an adverse effect on overall response because (1) therapy being withheld for myelosuppression, decreases the exposure to imatinib (2) myelosuppression may be a manifestation of reduced normal stem pool which is unable to manifest as full normal hematopoiesis after suppression of the abnormal clone[5]. The most common adverse event seen with Imatinib is myelosuppression, grade 3 or 4 neutropenia (absolute neutrophil count<1x10^9/L) and thrombocytopenia (platelet count <50x10^9/L) in up to 30% of patients, and anaemia in 5 to 15% of patients[6]. To evaluate cytopenias occurring in Imatinib treated CML patients and to plan to minimize and treat cytopenic complications early.

Materials and Methods

This cross sectional observational study having both descriptive and analytical components was done at the department of Haematology in Combined Military Hospital, Dhaka and Hematology OPD, Bangabandhu Sheikh Mujib Medical University (BSSMU). The study was carried out on 30 patients from October 2011 to September 2012. CML patients with Philadelphia chromosome positive, Treated with Imatinib regularly were included. Patients who are in accelerated or blastic phase of CML, and who are treated with Hydroxyuria, or not responding to Imatinib has been excluded from the study. All data and information were collected with the permission of the patients. Written informed consent was taken. Main outcome variables to be studied were clinical history, complete physical examination, complete blood count and bone marrow study. The cytopenias (anaemia, neutropenia and thrombocytopenia) has been graded according to the NCI common terminology criteria for adverse events version 3.0, which is a descriptive terminology utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

1. **Lt Col Lutfunnahar Khan**, MBBS, DCP, MCPS, FCPS, Classified Specialist in Pathology, CMH Jashore (*E-mail*: nahar_khan@yahoo.com) 2. **Lt Col Masuma Ahmed Salsabil,** MBBS, MCPS, FCPS, Classified Specialist in Pathology, CMH Ghatail **3. Dr Jannatul Ferdous,** MBBS, FCPS, Associate Professor of Pathology, Mugda Medical College Dhaka. 4**. Col Md Rezwonul Haque**, MBBS, FCPS, Classified Specialist in Surgery, CMH Jashore.

Table-I: Adverse event grading (severity) scale

Adverse Events	Grades				
	1	2	3	4	5
Haemoglobin Gm/dl	<LLN-10	<10-8	<8-6.5	<6.5	death
Total WBC count X10⁹/L	<LLN-03	<3-2	<2-1	<1	death
Neutrophil count X10⁹/L	<LLN-1.5	<1.5-1	<1-0.5	<0.5	death
Platelet count X10⁹/L	<LLN-75	<75-50	<50-25	<25	death
Bone marrow study	Mildly hypocellular or ≤ 25% reduction from normal cellularity for age	Moderately hypocellular or > 25% -≤ 50% reduction from normal cellularity for age	Severely hypocellular or >50-≤75% reduction from normal cellularity for age	-	death
LLN=Lower Limit of normal					

Data analysis was carried out by using Statistical Package for Social Sciences (SPSS). Univariate analysis was used to observe the frequencies, mean and standard deviation (SD) of different variables. Associations of different tests (Hb%, PC, TC, DC, PBF, myelocytes %, blast %) with other variables and within them were analyzed by Chi square test and p value less than 0.05 was considered as significant.

Results

A total of 30 diagnosed patients of CML on Imatinib were analyzed. Their ages ranged from 20 to 59 years with a mean age±SD of 38.96±9.37 years and majority 11(36.67%) of patients were from 30-39 years age group, 07(23.33) patients from age group of 40-49 years and 07(23.33) patients from age group of 50-59 years. Rest 05(16.67%) patients were from 20-29 years age group (Table-II). Out of 30 patients 22(73%) were male and 8(27%) were female with male to female ratio was 2.5:1. Table-III shows the clinical presentation of CML patients at the time of diagnosis found most of the patients presented with generalized weakness (83.3%), weight loss (53.3%), fever (26.7%), pain abdomen (36.6%) and fullness of abdomen (33.3%). Most of the patients presented with splenomegaly (90%) and anaemia (80%) followed by bony tenderness (33.3%) and hepatomegaly (26.7%). Table-IV shows the results of complete blood count during diagnosis of CML in chronic phase before and after starting treatment with Imatinib Mesylate.

Table-V shows types of cytopenias with their number and frequency after being treated with Imatinib. There were 24 (80%) cases with anaemia, 03 (10%) cases with leucopenia and 07 (23.33%) cases with thrombocytopenia. Some patients developed bicytopenia, like Anaemia+ Neutropenia in 03 (10%) cases, Anaemia + Thrombocytopenia in 05 (16.67%) cases and Neutropenia + Thrombocytopenia in 03 (10%) cases. Pancytopenia was found in 02 (6.67%) cases. Table-VI also shows number of patients developing cytopenia and the grading according to the NCI Common Terminology Criteria for Adverse Events v3.0. Most of the patients (66.67%) had grade 1 anaemia and grade 2 anaemia in 4 cases (13.33%). On the other hand, grade 1 neutropenia and thrombocytopenia in 4 (13.33%) and 5 (16.67%) cases respectively. There was no grade 3 or grade 4 cytopenia. Two patients (6.67%) developed pancytopenia. Table-V shows that bone marrow study was normal active or near normal marrow in 20 patients (66.67%). There was marrow hypercellularity in 03 (10%) cases and persistence of disease in 02 (6.67%) cases.

Table-II: Distribution of patients by age and sex (n=30)

Characteristics		Frequency	Percentage
Age in years	20-29	05	16.67
	30-39	11	36.67
	40-49	07	23.33
	50-59	07	23.33
Sex	Male	22	73.00
	Female	08	27.00

Table-III: Distribution of patients by clinical presentation (n=30)

		Frequency	Percentage
Symptoms	**Weakness**	25	83.3
	fever	08	26.7
	Abdominal fullness	10	33.3
	Pain in abdomen	11	36.6
	Weight loss	16	53.3
	Asymptomatic	04	13.4
Signs	**Anaemia**	24	80
	Bony tenderness	10	33.3
	Purpura	02	6.7
	Lymphadenopathy	01	3.3
	Hepatomegaly	08	26.7
	Splenomegaly	27	90

Table-IV: Distribution of patients by laboratory findings before and after starting Imatinib Mesylate therapy (n=30)

Parameters			Frequency	Percentage
Before starting Imatinib Mesylate	**Haemoglobin** (gm/dL)	≤6	--	--
		>6-9	13	43
		>9	17	57
	Total leucocyte count ($x10^9$/L)	≤50	02	6.67
		>50-100	10	33.33
		>100	18	60
	Basophil (%)	≤01	03	10
		>01	27	90
	Eosinophil (%)	≤04	20	66.67
		>04	10	33.33
	Myelocyte (%)	≤15	08	26.67
		15-30	14	46.66
		>30	08	26.67
	Blast (%)	≤05	16	53.44
		>05	14	46.66
	Platelet count ($x10^9$/L)	≤400	07	23.33
		>400	23	76.67
After starting Imatinib Mesylate	**Haemoglobin** (gm/dl)	>6.5	--	--
		<8-6.5	--	--
		<10-8	20	67.67
		>10	10	33.33
	Total leucocyte count ($x10^9$/L)	<1	--	--
		<2-1	--	--
		<3-2	1	3.33
		<4-3	2	6.67
		>4	27	90
	Neutrophil count ($x10^9$/L)	<0.5	--	--
		<1.0-0.5	--	--
		<1.5-1.0	2	6.67
		<4-1.5	4	13.33
		>4	24	80
	Platelet count ($x10^9$/L)	<25	--	--
		<50-25	--	--
		<75-50	2	6.67
		<150-75	5	16.67
		>150	23	76.66

Table-V: Distribution of patients by grades of cytopenias (n=30)

Cytopenia	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Anaemia	20(66.67)	04(13.33)	--	--	24(80)
Leucopenia	01(3.33)	02(06.67)	--	--	03(10)
Neutropenia	04(13.33)	02 (06.67)	--	--	06(20)
Thrombocytopenia	05(16.67)	02 (06.67)	--	--	07(23.33)
Anaemia + Neutropenia	--	--	--	--	05(16.67)
Anaemia + Thrombocytopenia	--	--	--	--	03(10)
Neutropenia + Thrombocytopenia	----	--	--	--	03(10)
Pancytopenia	--	--	--	--	02(6.67)

Table-VI: Distribution of patients by bone marrow morphology (n=30)

Bone marrow morphology	No of patients	Percentage
Normal active marrow	20	66.67
Marrow hypoplasia	03	10.00
Marrow fibrosis	01	3.33
Persistence of disease	02	6.66

Discussion

The development of effective tyrosine kinase inhibitors (TKIs) for patients with chronic phase of chronic myeloid leukaemia (CP-CML) has revolutionized the treatment of the disease. From 2000 onward Imatinib 400 mg daily became the preferred initial treatment[9]. In this study, total 30 patients were evaluated, the patients ranged from 23 to 56 years of age with a mean age of 38.96±9.37 years. Majority of the patients were in 30-39 years age group (36.67%), 07 patients (23.33%) in 40-49 yrs, %), 07 patients (23.33%) in age group of 50-59 yrs. Rest 5 patients (16.67%) were in 20-29 yrs age group. This result is nearly similar a previous study in Bangladesh by Yunus ABM[10], in a project enlisted 55 patients from 2005 to 2007. He found maximum patients were within the age of 34-43 was (30.9%) yrs, followed by 25-34 (29%) years. Out of 30 patients, 22 cases (73%) were male and 8 cases (27%) were female. Here Male: female ratio was 2.5:1. In one study by Mukibi JM, Nyirendra CM, Paul B, Adewuyi JO, Mzula EL, Malata HN., Chronic myeloid leukaema in central Africans, published in East African Medical Journal, 150 CML patients were studied. Male predominated in a ratio of 1.5:1. The peak age incidence of 47% occurred between 21 to 40yrs[11].

The common clinical presentation of CML (chronic phase) patients at the time of diagnosis were generalized weakness (83 .30%), weight loss V (53.3%), pain abdomen (36.6%), and fullness of abdomen (33.3%). The other less common symptoms were fever (26.7%) and bleeding manifestations (6.7%). In this study, 04 (13.4%) patients were asymptomatic. Physical examination of 30 patients at the time of diagnosis revealed that most patients presented with splenomegaly (90%), anaemia (80%), bony tenderness (33.33%) and hepatomegaly (26.7%). Savage DG, Szydlo RM, Goldman JM reviewed clinical features at diagnosis in 430 CML patients at a referral centre over a 16-year period[12]. Symptoms such as fatigue (83%) and weight loss (61%) were associated with greater degrees of leucocytosis and splenomegaly and lower haemoglobin levels. At the time of diagnosis, 43% patients had haemoglobin level from 6 to 9 gm/dl and the rest 57% had more than 9 gm/dl, out of total 30 patients. Total WBC count was >100x10^9/L in 18 (60%) cases and 50-100x10^9/L in 10 (33.3%) cases. In peripheral blood film study myelocyte percentage was less than 15% of WBC count in 08 (26.67%) patients, 15-30% myelocytes in the highest 14 (46.66%) cases and more than 30% in 08 (26.67%) cases. Philadelphia chromosome was found in all 30 cases and they were being treated with Imatinib Mesylate 400 mg daily for varying period. Out of these, 16 patients developed some form of cytopenia. Anaemia was found in 24 (80%) cases, leucopenia in 03(10%), neutropenia in 06(20%), thrombocytopenia in 07 (23.33%) cases. Bicytopenia was also found as follows, anaemia + thrombocytopenia in 05(16.67%) cases, anaemia + neutropenia in 3(10%) and neutropenia + thrombocytopenia in 03 (10%) cases. Pancytopenia was found only in 02(6.67%) cases. Similar type of result was found in another study by T. Roshni Paul

et al from January 2008 to june 2009[13]. In that study anaemia was the commonest cytopenia followed by thrombocytopenia and neutropenia. There were 18 patients of bicytopenia and 13 patients of pancytopenia out of 60 cytopenic patients. A combination of anaemia and thrombocytopenia was the most commonly noted bicytopenia.

Patients developing cytopenia were categorized according to the NCI Common Terminology Criteria for Adverse Events v3.0. for Adverse Event (AE) reporting. In this study most of the patients had grade 1 anaemia in 20(66.67%) cases and grade 2 anaemia in 4 (13.33) cases. On the other hand, grade1 leucopenia was found in 1(3.33) cases, grade 2 leucopenia in 02(6.67%) cases. Grade 1 thrombocytopenia was present in 05(16.67%) cases and grade 2 in 02(6.67%) cases. There was no grade 3 or grade4 cytopenia. Bone marrow study showed normal active marrow in 20 (66.67%) patients, hypocellularity in 03 (10%) and persistence of disease was in 02(6.66%).

Conclusion

Imatinib has revolutionized the concept of molecularly targeted therapies by demonstrating that a small molecule inhibitor of a tyrosine kinase can fundamentally alter the pathobiology of a leukaemia. Regarding adverse effects, various degrees of cytopenia may occur in a few patients of CML on Imatinib. The cause of the cytopenia in patients treated with Imatinib is varied and the marrow morphology could be different in each case. Regular haematologic follow-up with blood counts and if necessary, bone marrow studies are required for patient management; so that the drug may be withheld or dose modified, as per individual needs.

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